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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/849,498	YANG ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *17-43,45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,44 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/2005, 4/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-48 are pending. Claims 17-43 and 45-47 are withdrawn. Claims 1-16, 44 and 48 are under examination.

Election/Restrictions

Applicant's election of Group I in the reply filed on 16 March 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 17-43 and 45-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 16 March 2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "physiological" and "non-physiological" in claim 2 are relative terms which render the claim indefinite. The terms "physiological" and "non-physiological" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, it is unclear whether certain salt and pH conditions found in certain cells and microenvironments within cells (such as in cell organelles) would be considered physiological or non-physiological conditions

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8-11 and 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Schacht et al.

Applicants claim an article for delivering a drug and a nucleic acid comprising: a nanoparticle having a first portion capable of associating a nucleic acid and a second

portion capable of associating a drug (claim 1). Applicants further claim wherein the nucleic acid is DNA (claim 4), and wherein the article is in a composition with a pharmaceutically acceptable carrier (claim 10). Applicants also claim wherein the nanoparticle is capable of associating/disassociating with a nucleic acid and a drug under non-physiological/physiological conditions, is capable of passing through a cell membrane, is stable at a concentration of greater than 5 mg/L, and comprises a graft co-polymer having a backbone including tertiary amines (at least a portion of the tertiary amines quarternized and bound to a hydrophobic side chain) (claims 2, 3, 8, 11). Applicants further claim limitations wherein the polymeric backbone comprises a copolymer of quaternized and non-quaternized tertiary ammonium groups and wherein the polymeric backbone comprising a copolymer of quaternized and non-quaternized tertiary ammonium groups further comprises an ester linkage, a polyester, and a polyether (claims 13-16).

Applicant provides a broad description in the specification for how molecules may be associated and dissociated with one another for the claimed invention. Applicant recites: "A first molecule may be "associated" with a second molecule, under set conditions, if the two molecules move together as a unit under these conditions. For example, the two molecules may be immobilized with respect to each other. The two molecules may be covalently or ionically bonded, may be joined by Van der Waal's forces or magnetic forces or one molecule may be physically contained or trapped by the second molecule or a collection of second molecules" [instant specification ¶ 0048]. Applicant further recites: "A first molecule may be "disassociated" from a second

molecule or article with which it is associated. Disassociated means that the first molecule can move independently of the second molecule. The first molecule can also be disassociated from a second molecule or from an article if the second molecule or article degrades or is broken down so that it is no longer linked to the first molecule" [instant specification ¶ 0049].

Schact et al, (WO/98/19710, published 14 May 1998, "Delivery of Nucleic Acid Material to Target Cells in Biological Systems", see whole document) teach an amphoteric polymeric nanoparticle with a hydrophilic portion capable of associating with nucleic acid (DNA) and a hydrophobic portion capable of associating with a drug and capable of directing the particle through cell membranes. For example, Schact et al state in order to adapt biologically inert polymer material such as pHPMA to enable interaction with cell membranes for bringing about transfection, "membrane active lipids, e.g. oieyl, pH-responsive amphipathic peptide helices or constitutively-active amphipathic helices (i.e. not dependent on pH for induction of membrane activity), may be incorporated during synthesis. In addition, there is also a possibility of incorporating agents to provide internalization following receptor-binding. A particular example of such an agent is the integrin-binding tripeptide RGD (arginine-glycine-aspartic acid) but other materials, probably also integrin-binding functionalities, could also be used." (p. 12, ¶ 3, lines 1-10).

In addition, Schact et al teach wherein the nanoparticle comprises a graft co-polymer having a backbone including non-quarternized and quarternized tertiary amines bound to a hydrophobic side chain and wherein the backbone further comprises an

ester linkage, a polyester, and a polyether. For example, Schact et al recite polymers may be linked to one or more hydrophilic polymers to form graft block copolymers, by providing reactive groups spaced along the length of the cationic polymers. "In some embodiments, the preferred reactive groups for bringing about this coupling, either at the ends or on side chains along the main polymer backbone, are conveniently provided by reactive amine or thiol groups. The present example, shown in the diagram of FIGURE 3 of the accompanying drawings, describes the preparation of graft copolymers by the reaction of poly(HPMA)-COOH with cationic polymers bearing primary amino groups in their side chains [poly(Lys), poly(Ma-Gly- NH-(CH2)-NH2, poly(Ma-NH-(CH2)-NH2 etc.]" (p. 35, lines 13-23 and p. 55, claim 10). In addition, Schact et al teach the graft copolymer will be based on copolymers of N-2-hydroxypropylmethacrylamide (HPMA) with activated esters of N-methacryloylated peptides" (p.6, lines15-17).

Furthermore, Schact et al teach a stable nanoparticle concentration which meets the limitations of instant claim 8, reciting "a very efficient stabilization to albumin disruption has been determined, using the reactive polymer at concentrations of 300 ug/ml" (p.19, ¶ 4, lines 26-28).

Although Schact et al do not explicitly discuss the ability of their complex to cross the blood/brain barrier, Schact et al teach properties of their complex which would inherently make the complex capable of crossing the blood/brain barrier. For example, Schact et al teach a complex comprising nanoparticles for delivery of nucleic acid and a drug which is stablilized by a hydrophilic coating which provides for protection "in the

course of in vivo gene therapy when circulating in the plasma following administration by intravenous injection" (sentence spanning p.5-6). In addition, Schact et al contemplate attaching molecules to the nanoparticles which provide for specific interactions and passage through membranes. For example, Schact et al recite molecular entities that may be carried by the cationic polymer core include "cell-receptor targeting moieties and/or other specific bioactive agents"(p.6, ¶ 2, lines 1-7). Although Schact et al do not explicitly discuss the ability of their complex to cross the blood/brain barrier, the ability to persist in the plasma (blood) as well the ability of the complex to target and enter specific membranes would inherently make the particle of Schact et al capable of crossing the blood/brain barrier.

In addition, Schact et al do not explicitly teach cancer drugs (claim 5) but do teach incorporation of a variety of drug molecules and further contemplate "the carrier vehicles may be used for targeted transfection of cancer cell lines (p.8 ¶ 4, lines 7-9).

Therefore Schact et al teach applicant's invention and anticipate claim limitations for claims 1-4 and 8-11 and 13-16.

Claims 1-4, 6, 8, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al ("Novel Branched Poly(Ethylenimin)-Cholesterol Water-Soluble Lipopolymers for Gene Delivery" in Biomacromolecules, published 9/7/2002, Vol. 3 p. 1197-1207, see whole document).

Applicant's invention is as described in the above 35 USC 102(b) rejection. In addition, applicants claim wherein the article forms a micelle and wherein the nanoparticle comprises a graft co-polymer having a backbone including non-quarternized and quarternized tertiary amines bound to a hydrophobic side chain comprising cholesterol. Wang et al teach the amphoteric nanoparticle capable of associating a nucleic acid and a drug and further wherein the nanoparticle comprises a graft co-polymer having a backbone including non-quarternized and quarternized tertiary amines bound to a hydrophobic side chain comprising cholesterol (see abstract and p.1200, ¶ 3, lines 1-28 and Fig.1 & legend). Furthermore, Wang et al teach wherein the nanoparticle is stable at a concentration of greater than 5 mg/L which meets the limitations of claim 8. For example, Wang et al recite "plasmid was condensed at DNA concentration of 0.1 mg/mL and the polymer concentration of 0.016-0.472 mg/mL, which are below the critical micellar concentration of these lipopolymers and that the critical micellar concentration of two versions of the polymers were 0.497 and 1.33 mg/mL (p.1205, ¶ 2, lines1-5) all concentrations which are orders of magnitude higher than the claimed concentration of 5 mg/L.

Therefore Wang et al teach applicant's invention and anticipate claim limitations for claims 1-4, 6, 8, 11 and 12.

Claims 1-16, 44 and 48 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Lollo et al, (USPGPub 2003/0134420A1, filed 2 August 2002, published 17 July 2003, see whole document).

Applicant's invention is as described in the above 35 USC 102(b) rejections for claims 1-4, 6 and 8-16. In addition, applicants claim the article in claim 1 wherein the drug is a cancer drug, wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle, and wherein the article is in a composition with a pharmaceutically acceptable carrier (claims 5, 7 and 10). Applicants also claim a composition comprising: a nanoparticle, a non-nucleic acid drug associated with a first portion of the nanoparticle, and a nucleic acid associated with a second portion of the nanoparticle and a kit comprising: a container including an amphoteric polymeric nanoparticle, a drug associated with a first portion of the nanoparticle, a nucleic acid associated with a second portion of the nanoparticle, and instructions for administering the nanoparticle to a subject (claims 44 and 48).

Lollo et al teach a micelle complex comprised of amphoteric nanoparticles having a hydrophilic portion associating with DNA and/or cancer drugs and a hydrophobic portion capable of associating with cancer drugs and capable of passing through a cell membrane and capable of being directed to specific membranes by receptor-mediated targeting. In addition, Lollo et al contemplate a multidomain complex which can accommodate nucleic acids either on the interior or exterior and can accommodate drugs either on the interior or exterior. For example, Lollo et al recite: "Typically, the center domain (Zone I of FIG. 1) contains the anionic agent. Examples of anionic agents

include nucleic acids, negatively charged drugs and other small molecules capable of being delivered via a polyplex through a cellular boundary or lipid membrane" (¶ 0032, lines 2-4 and especially ¶ 0031-0038).

Furthermore, Lollo et al anticipate using their invention to treat a subject and although do not explicitly recite "instructions", it would be inherent that any treatment plan for treating a human subject would inherently require instructions. For example, Lollo et al recite "A method for treating a subject comprising administering to said subject an effective amount of a penetration enhancer and a polyplex comprising a nucleic acid, a cationic backbone moiety, a hydrophobic moiety, and a hydrophilic moiety, such that said subject is treated" (Lollo et al claim 58, 59 and 68). Lollo et al anticipate using the complex to deliver genes and drugs *in vivo* and thus anticipate claims 10, 44 and 48.

Furthermore Lollo et al teach an article as in claim 1 wherein the article forms a micelle (claim 6) and further teaches wherein a drug is associated with an interior of the micelle and a nucleic acid is associated with an exterior of the micelle (claim 7). For example, Lollo et al teaches partially hydrophobic conjugates also may be used since they possess moieties that preserve sufficient water solubility (since purely hydrophobic molecules are water insoluble). These conjugates can be made up of two different types of grafts, hydrophilic moieties to maintain adequate water solubility (`A`), and hydrophobic moieties (`B`) to introduce a domain with binding and micelle formation properties. In one embodiment, the polymer is designed by grafting two or more of these elements onto a cationic backbone moiety (e.g., a cationic polymer, `C`). A

suitable grafting element, or hydrophilic moiety for this approach is PEG, which promotes solubility and steric shielding. Another suitable grafting element is any hydrophobic moiety, as described above, which may form domains with binding capabilities. These two or more types of grafting elements can then be randomly distributed along a cationic backbone moiety during the grafting step (¶ 0067, lines 1-6).

In addition, Lollo et al teaches an article as in claim 1 wherein the nanoparticle is stable at a concentration of greater than 5 mg/L because Lollo et al recites "polyplex concentration are reported by DNA content and were 10 ug/ml" which reads on the instant claim 8.

Furthermore, Lollo et al teach an article as in claim 1 wherein the nanoparticle comprises a graft co-polymer having a backbone including tertiary amines, at least a portion of the tertiary amines quaternized and bound to a hydrophobic side chain (claim 11), and further teaches wherein the hydrophobic side chain comprises cholesterol (claim 12). For example, Lollo et al teaches FIG. 11 shows the structure of grafted polymers with two hydrophobic domains per PEG chain. FIG. 11a shows a hydrophobic domain between the cationic domain and the surface domain. FIG. 11b shows a hydrophobic domain positioned at the terminus of a surface (e.g., hydrophilic) domain, and between the surface (e.g., hydrophilic) and cationic domains (¶ 0023, lines 1-3).

Therefore Lollo et al teach applicant's invention and anticipate claim limitations for claims 1-16, 44 and 48.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is 571-270-3053. The examiner can normally be reached on Monday-Friday, 7:30 AM-5:00 PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert/AU1636